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Regression of "Gray Zone" Exercise-Induced Concentric Left Ventricular Hypertrophy During Prescribed Detraining

To the Editor: Left ventricular hypertrophy (LVH) may develop in response to exercise training. In extreme cases, exercise-induced LVH (EI-LVH) may be difficult to differentiate from clinically relevant conditions such as hypertrophic cardiomyopathy (HCM). A valuable clinical pathway integrating aspects of the medical history, physical examination, 12-lead electrocardiogram (ECG), and noninvasive imaging has been developed for determining the etiology of such "gray-zone" hypertrophy (1). Although this algorithm is useful, it does not always produce a definitive diagnosis. In cases that remain ambiguous, prescribed detraining is recommended (2).

The geometry of EI-LVH is variable with endurance/isotonic exercise leading to eccentric hypertrophy and strength/isometric exercise leading to concentric hypertrophy. Eccentric EI-LVH, balanced chamber enlargement and wall thickening, is typically distinct from HCM. In contrast, concentric EI-LVH, characterized by increased relative wall thickness, is morphologically similar to HCM. Thus, the significance of concentric LVH among athletic patients is often a source of clinical uncertainty. Prior studies documenting the regression of LVH following detraining have largely examined elite athletes with eccentric EI-LVH over variable time periods of detraining (3,4), leaving the response to detraining among athletes with concentric EI-LVH incompletely understood. We therefore examined the myocardial response to 6 months of prescribed detraining among a group of collegiate male football players with "gray-zone" concentric EI-LVH.

Participants were recruited from the Harvard Athlete Initiative, a longitudinal program designed to evaluate myocardial structure and function among collegiate athletes. Eligibility criteria for this study included: 1) normal cardiac structure without LVH at the time of university matriculation; 2) concentric EI-LVH at the immediate conclusion of the 4-year collegiate athletic career; and 3) willingness to participate in a prescribed detraining program. Eligible participants completed a 6-month period of prescribed detraining during which exercise training was limited to <2 hr/week. None of the participants took anabolic steroids during their college athletic careers and none reported taking any medications during the detraining period. Twelve-lead ECGs were obtained on all athletes at all time points. ECG voltage was quantified by the summation of the R- and S-wave voltages in all precordial leads as previously described (3). Parameters of left ventricular (LV) structure were assessed by 2-dimensional echocardiography (Vivid-I, General Electric, Milwaukee, Wisconsin) at 4 time points: college matriculation (baseline), completion of competitive collegiate football (peak fitness), and after 3 and 6 months of detraining. Concentric LVH was defined as LV wall thickness ≥12 mm, LV mass >126 g/m (5), and relative wall thickness >0.42. Echocardiographic measurements were made by study investigators (R.B.W., A.L.B.) blinded to study time point. Correlation coefficients (r^2) defining interobserver variability (simple linear regression) were 0.963 and 0.959 for LV wall thickness and mass, respectively. Repeated measures analysis of variance with Bonferroni's multiple comparison correction was used to assess significance of interval changes across study time points.

Five males (age 21 ± 1 year, height 1.9 ± 0.07 m) met eligibility criteria and completed the detraining protocol. Each individual had normal cardiac structure (LV mass 113 ± 8 g/m, LV wall thickness 10.5 ± 0.5 mm) upon college matriculation and demonstrated concentric EI-LVH at the completion of collegiate athletics (LV mass 139 ± 7 g/m, $p < 0.001$; LV wall thickness 12.4 ± 0.5 mm, $p < 0.001$). Systolic blood pressure declined from peak training through 6 months of detraining (peak 137 ± 10 mm Hg vs. 3 months 109 ± 9 mm Hg vs. 6 months 108 ± 6 mm Hg, $p < 0.001$) while diastolic blood pressure and body mass were unchanged.

Significant regression of LV mass, LV wall thickness, and left atrial size occurred during detraining (Fig. 1). Although regression was observed at 3 months, 6 months was required for complete normalization of all cardiac parameters. Additionally, there was a trend toward an increase in LV diastolic dimension after detraining (peak 52.4 mm vs. 6 months 53.9 mm, $p = 0.08$). Comparison of ECG voltage across the detraining period showed a trend toward voltage regression (peak 132 ± 28 mm vs. 3 months 122 ± 21 vs. 6 months 119 ± 19 mm, $p = 0.09$).

Prior studies examining the LV response to exercise cessation have focused on eccentric EI-LVH and have not standardized the duration of detraining. Maron et al. documented regression of eccentric EI-LVH among Olympic athletes over 6 to 34 weeks (mean 13 weeks) (3). The largest detraining report included 40 elite Italian male athletes with eccentric LVH (LV dimension 61.2 ± 2.9 mm, LV wall thickness 12.0 ± 1.3 mm) (4). These athletes demonstrated complete normalization of wall thickness and significant but incomplete reduction in cavity dilation after 5.8 ± 3.6 years of detraining.

Data defining the response of concentric EI-LVH, the geometric form that most closely resembles HCM, to prescribed exercise cessation are lacking. Thus, clinical implementation of prescribed detraining in this setting is problematic for several reasons. First, there are insufficient data documenting the extent of regression of concentric EI-LVH. Second, the time required for clinically meaningful detraining remains unknown. The present study provides novel data that address both of these issues. We have shown that concentric EI-LVH is a dynamic process that can regress fully following removal of the training stimuli. In addition, we have shown that 6 months of detraining may be necessary to produce complete normalization of LV structure.

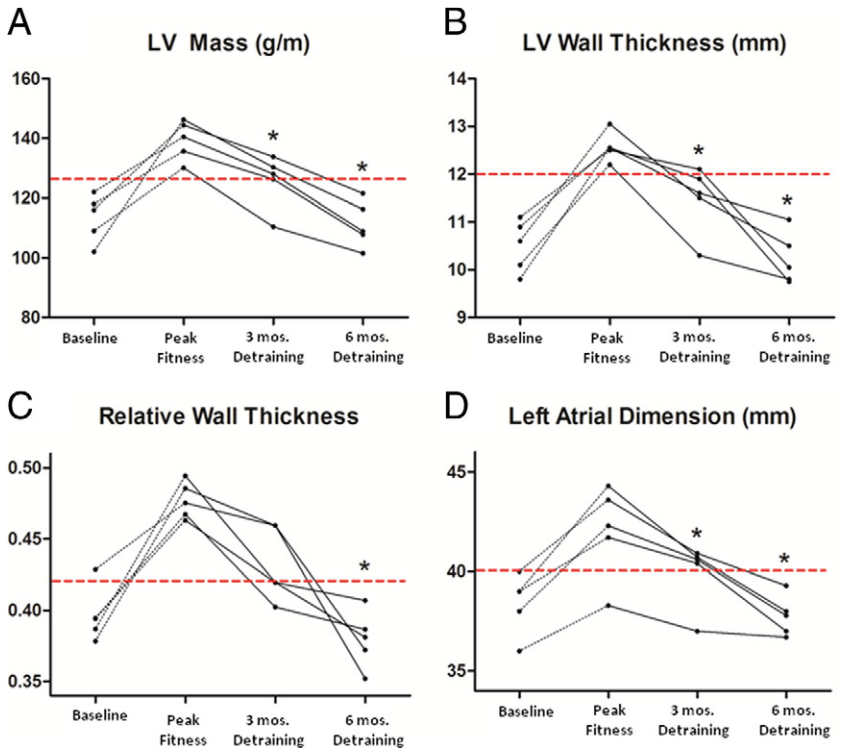

Figure 1 **Left Ventricular and Left Atrial Changes With Exercise Training and Subsequent Prescribed Detraining**

Changes in left ventricular (LV) mass **(A)**, LV wall thickness **(B)**, relative LV wall thickness **(C)**, and left atrial dimension **(D)** among male football players with "gray-zone" concentric LV hypertrophy (n = 5) during a 6-month period of prescribed detraining. **Dashed lines** represent selected cutoff values for normal LV mass (<126 g/m), LV wall thickness (<12 mm), LV relative wall thickness (<0.42 mm), and left atrial size (<40 mm) (5). LV mass was calculated using the American Society of Echocardiography recommended linear dimension formula with adjustment for height (meters) (5). LV wall thickness was calculated as the average of interventricular septum and posterior wall measurements derived from parasternal long-axis 2-dimensional echocardiographic images. Relative wall thickness was calculated as: (interventricular septum thickness + posterior wall thickness)/LV end-diastolic dimension. Left atrial dimension was measured as the anterior-posterior major dimension from the parasternal long-axis 2-dimensional echocardiographic images. *$p < 0.05$ compared with preceding time point.

Pathologic LVH, most commonly HCM, is an important cause of sudden cardiac death among young competitive athletes, while EI-LVH is considered to be a benign physiological phenomenon. Thus, the assessment of the athlete with LVH of indeterminate etiology is a task with important clinical implications. Although clinical assessment combined with noninvasive imaging is often capable of differentiating pathologic from EI-LVH, prescribed detraining is necessary in some cases. Findings from the present study may assist clinicians contemplating a detraining directive by providing data documenting the time course and completeness of concentric LVH regression.

There are limitations of this study. First, we studied a small number of athletes and further confirmatory work is warranted. Second, we studied relatively young athletes and are thus unable to comment about whether our observations can be applied to older individuals with more extensive prior exercise exposure. Nonetheless, we studied National Collegiate Athletic Association athletes, a large population in which the clinical dilemma of distinguishing physiologic from pathologic hypertrophy occurs with relatively high frequency. Finally, the use of cardiac magnetic resonance in addition to echocardiography may allow for more precise quantification of changes in LV wall thickness and mass in future studies.

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